

ACE Dwindle and Bradykinin Amelioration: The Avant-Garde Miscreant in the Pathophysiology of COVID-19

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Abstract

Background: COVID-19 has been talk of the town for medical fraternity at present as to date we are unable to find the exact treatment of the disease as the pathophysiology of the ailment is still not revealed completely. The new researches are pointing towards bradykinin which is a short chain of amino acids made up of kinin group of proteins that causes inflammation as main culprit of the disease. As the coagulation part of the COVID-19 is unknown and it is resistant to classical treatment of coagulopathies. In this article, we have postulated the bradykinin behind the coagulopathies through few basic blood analysis, different theoretical concepts and hypotheses affirming the certitude.

Materials and Methods: We studied bradykinin linked with COVID-19 and its general, physiological and pathological functions in subjects by checking their Angiotensin converting enzyme (ACE) levels in blood and has compared related studies on PubMed, Google Scholar and CDCs, showing linkage of coagulation in COVID-19 patients with bradykinin's major role behind it.

Results: ACE levels were low in group of patients who were COVID-19 positive and have developed coagulopathies as a complication of the disease which gives an indirect idea of high levels of bradykinin in SARS-COV-2 infected patients, hence proving the idea behind the indignation.

Conclusion: The patients with coagulopathies happens to have a bradykinin storm and treating high levels of bradykinin might be an effective way of treating coagulopathies rather than treating it with conventional methods.

Keywords: *Bradykinin; Bradykinin Storm; COVID-19; Angiotensin Converting Enzyme (ACE); Kinin-Kallikrein System; RAAS; Coagulopathies; Factor XII*

Introduction

COVID-19 has been talk of the town for medical fraternity at present as to date we are unable to find the exact treatment of the disease as the pathophysiology of the ailment is still not revealed completely. The new researches are pointing towards bradykinin which is a short

chain of amino acids made up of kinin group of proteins that causes inflammation as main culprit for the disease. As the coagulation part of the COVID-19 is unknown and it is resistant to classical treatment of coagulopathies. If we study bradykinin in more depth, bradykinin is known to be notorious for inflammation and cause small vessels to dilate by the formation of endothelium-derived hyperpolarizing factor, prostacyclin and nitric oxide. It also leads to venous constriction by prostaglandin F2 causing leakage into capillary beds as the pressure in the capillaries is increased. It is also known to be increased in people taking ACE inhibitors as low levels of ACE leads to inhibition of bradykinin’s degradation. Bradykinin can also produce bradykinin storm and can lead to various symptoms unexplained to date in COVID-19 patients and mostly known pathologic reasoning has limited to cytokines assumed to be the probable reason behind the clinical presentation of the disease. Howbeit no ratification has been given by any sanction bodies such as FDA, WHO, or any research institute about exact pathology of the disease. Moreover, the winters are approaching and the possibility of co-infection of Influenza with Corona can be expected, which would be a greater toll on health care authorities and the morbidity of these diseases together can be significantly high. Moreover, we very well know that the infection is proving to be fatal in patients with any chronic illness or co-morbid condition. Hence, we must pace up ourselves to get the exact pathophysiology of the disease in order to find the targeted treatment against the virus and understand bradykinin’s role in the disease would be really beneficial to know the course of the disease in due time. As every day we are seeing new symptoms, complications and changing course of disease, such as coagulopathy which is recently reported with COVID-19, a complete cure is quite a difficult job to find in a short span of time without knowing the proper course of the disease. This is just like shooting on the target without knowing where the target lies and we have no time for hit and trial methods as mortality rate is increasing and infection is spreading like fire in the forest. So time and energy should be invested in understanding the basics of the disease which is its pathology. As without understanding a disease’s pathology it is impossible to develop a sure shot treatment.

Aim of the Study

The soul aim of our research is to establish relation between bradykinin and coagulopathies in patients infected with SARS-COV-2 and understand the pathophysiology of COVID-19 in a better way.

Materials and Methods

Patients infected with SARS-COV-2 who developed coagulopathies were investigated for ACE levels in their blood. 2 groups were made and were labeled as group A and group B and their ACE levels were checked (The normal range of ACE levels is 8 to 53 microliters for adults) with few other peculiarities taken into consideration which are explained as follows: Group A had total number of 17 patients investigated out of which 11 were males and 6 were females. Their age bracket was 45 - 55 years without any co-morbidities or chronic illness. Out of 17 subjects, 7 males and 3 females had their ACE levels on slightly lower side and all of them developed coagulopathies as complication of COVID-19. Group B had the same age bracket with in total 7 patients out of which 4 were males and 3 were females, whom ACE levels were completely under normal range and out of them only 1 female developed coagulopathy.

We also compared related studies on PubMed, Google Scholar and CDCs, showing linkage of coagulation in COVID-19 patients with bradykinin’s major role behind it. With the received data, the normal and abnormal physiology of bradykinin in different physiological pathways was studied.

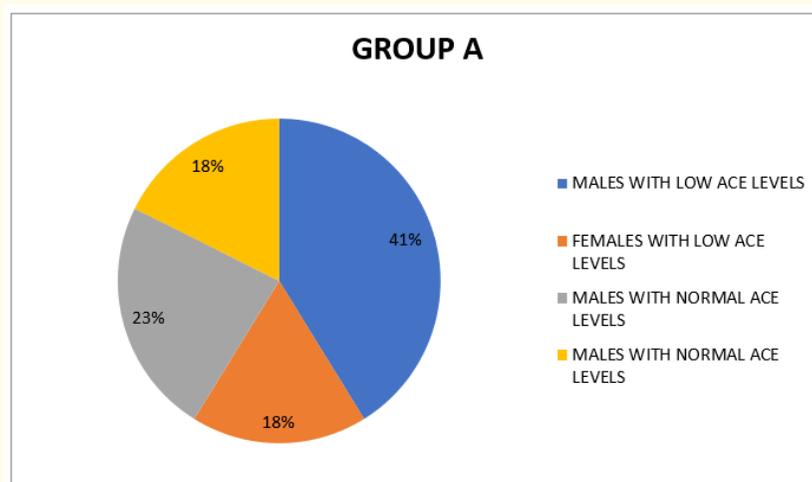


Figure 1: Group A: Distribution of patients depicting ACE levels with coagulopathies.

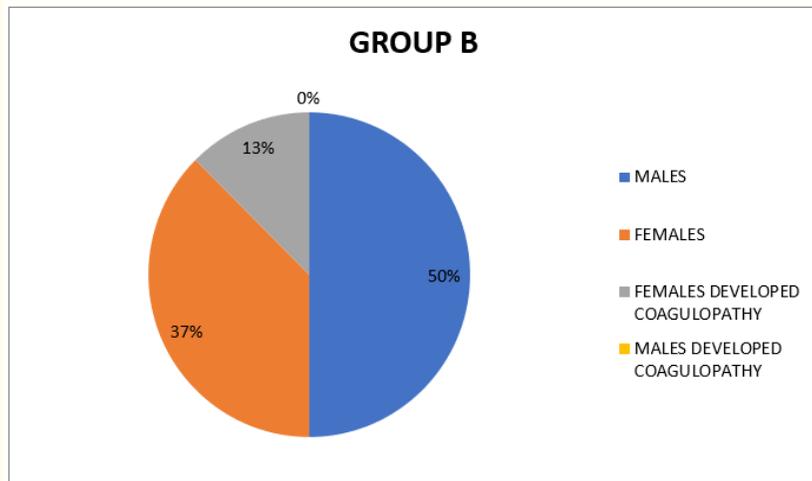


Figure 2: Group B: Distribution of patients depicting normal ACE levels developing coagulopathies.

Results and Discussions

Our findings were surprising and striking as the patients who were having normal ACE levels out of them developing coagulopathies was only one female patient in comparison to our 17 patients who had coagulopathy and out of them 10 patients had low levels of ACE, making 58.82%, of the total patients involved in study of group A.

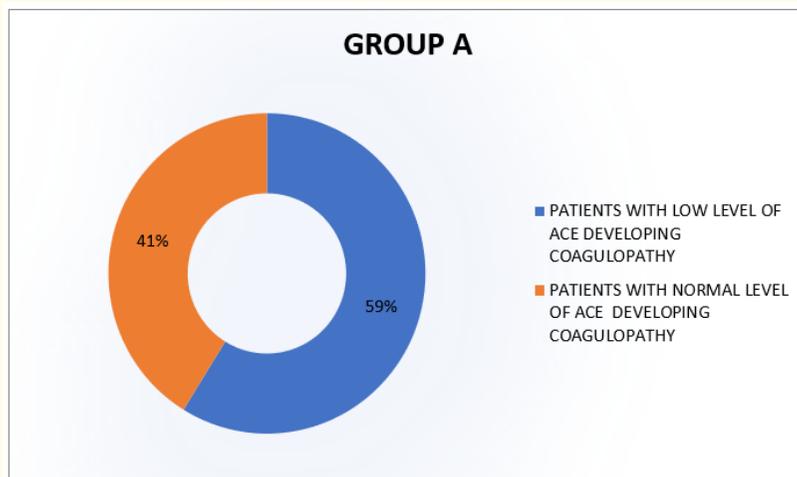


Figure 3: Group A: Distribution of patients in percentage depicting normal and low ACE levels with coagulopathies.

We really wanted to check the bradykinin levels and C1 levels in these patients but due to logistic limitations we were not able to do so.

But if we throw some light on the physiological functions of bradykinin and its relation with ACE, we know that Bradykinin is known to cause small vessels to dilate by the formation of endothelium-derived hyperpolarizing factor, prostacyclin and nitric oxide. It also leads to

venous constriction by prostaglandin F2 causing leakage into capillary beds as the pressure in the capillaries is increased. We also know that bradykinin levels are increased in people taking ACE inhibitors by hampering its inhibition.

The kinin-kallikrein system makes bradykinin by proteolytic cleavage of its kininogen precursor, high-molecular-weight kininogen by the enzyme kallikrein and also the fibrinolytic enzyme plasmin generate bradykinin after HMWK cleavage. Bradykinin is broken down by three kininases but angiotensin-converting enzyme (ACE) is the most studied among all.

If we see the effects of bradykinin, then it is a potent endothelium-dependent vasodilator and mild diuretic, which may cause a lowering of the blood pressure. It also causes contraction of non-vascular smooth muscle in the bronchus and gut, increases vascular permeability and is also involved in the mechanism of pain.

During inflammation, it is released locally from mast cells and basophils during tissue damage. Specifically in relation to pain, bradykinin has been shown to sensitize TRPV1 receptors, thus lowering the temperature threshold at which they activate, leading to loss of sensation of pain.

The secretion of bradykinin in new borne cause the closure of the ductus arteriosus, making ligamentum arteriosum between the pulmonary trunk and aortic arch. It also plays a role in the closure of the umbilical arteries and vein.

The bradykinin has receptors such as the B₁ receptor which is expressed only as a result of tissue injury and is known to play a role in chronic pain. This receptor has been also described to play a role in inflammation. It has been shown that the kinin B₁ receptor helps neutrophil by the chemokine CXCL5 production and endothelial cells have been described as a potential source for this B₁ receptor-CXCL5 pathway. The B₂ receptors participate in bradykinin's vasodilatory role. The kinin B₁ and B₂ receptors belong to G protein coupled receptors.

As the ACE levels are low in our patients who developed coagulopathy, it is highly expected that these patients must have had high levels of bradykinin in their body as the policeman to knockout the bradykinin is not in its enough quantity, leading to bradykinin storm which leads to its overexpression of function converting the physiological action into pathological adverse complication. The fuel in the fire is added by the cytokinin storm as well, leading to complete shutdown of an organism. For example, as discussed above bradykinin cause the increase in vascular permeability, the buildup of bradykinin can lead to capillary leak in lungs and fill them with fluid and cause pneumonia.

The connection between the Renin-Angiotensin-Aldosterone System (RAAS) and the Kinin-kallikrein system where decrease in ACE leads to more bradykinin which further leads to angioedema with involvement of factor XII.

The eye catching aspect over here is that the vascular leak leads to activation of factor XII and plasminogen. Moreover, we see a vicious cycle, where increase in bradykinin leads to formation of factor XII and increased factor XII lead to more formation of bradykinin. Bradykinin binds to its receptors on endothelial cells and increased vascular permeability allows extravasation of coagulation factors and tissue factor expressed in the extravascular space can initiate coagulation.

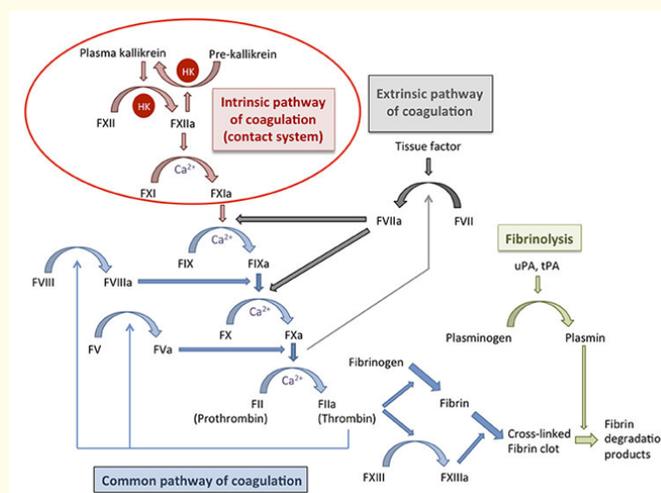


Figure 4: Depiction of relation between bradykinin and coagulation factors.

In COVID-19 patient also an immune response is generated against the viral infection to fight against it and cause activation of neutrophil and mast cells. This activation of these notorious elements apart from their function like chemotaxis, phagocytosis, anti-microbial and pro-inflammatory traits also helps in formation of bradykinin. The mast cell degranulation later on may trigger Factor XII activation, triggering the vicious cycle again as before.

Conclusion

We would like to conclude that bradykinin needs to be taken more seriously as the factor behind the pathophysiology of the COVID-19 and must be studied in larger cases of the disease to understand the pathophysiology of the disease more profoundly and in enthralled manner. The coagulation complications in COVID-19 cannot be treated with classical anti-coagulation treatment as the pathophysiology of coagulation in this disease is different to that we see in our normal practices. The bradykinin levels needs to be checked in the patients infected with SARS-COV-2 and consummate bradykinin workup should be done. Extensive researches should be encouraged and supported in understanding the role of bradykinin and anti-bradykinin therapies must be tested to find out the results, which we think will be really promising. We also have FDA approved anti-bradykinin therapies already and those are used in number of ailments, which can be an alternative treatment against SARS-COV-2 after evidence based researches proving the pathological dimensions.

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